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(71) Applicant (for all designated States except US): **HETERO DRUGS LIMITED** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500 018, Andhrapradesh (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PARTHASARADHI, Reddy, Bandi** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500 018, Andhrapradesh (IN). **RATHNAKAR, Reddy, Kura** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN). **RAJI, Reddy, Rapolu** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN). **MURALIDHARA, Reddy, Dasari** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN). **Srinivas, Reddy, Itiyala** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhrapradesh (IN).

(74) Common Representative: **HETERO DRUGS LIMITED**; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E. Balanagar, Hyderabad 500 018, Andhrapradesh (IN).

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**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
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(54) Title: NOVEL CRYSTALLINE FORMS OF TEGASEROD MALEATE

(57) Abstract: The present invention relates to novel crystalline forms to tegaserod maleate, to processes for their preparation and to pharmaceutical compositions containing them.

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## NOVEL CRYSTALLINE FORMS OF TEGASEROD MALEATE

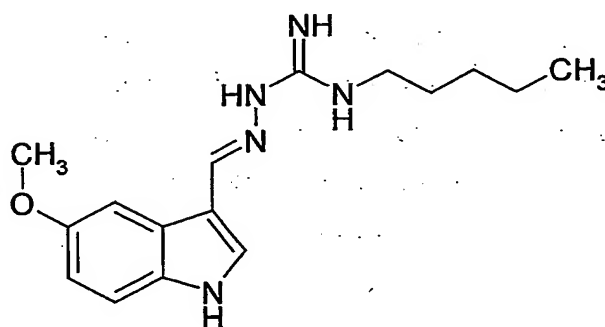
### FIELD OF THE INVENTION

5           The present invention relates to novel crystalline forms of tegaserod maleate, to processes for their preparation and to pharmaceutical compositions containing them.

### BACKGROUND OF THE INVENTION

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EP Patent No. 0 442,378 describes, along with other compounds, the compound (1)



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or 2-[(5-Methoxy-1H-indol-3-yl)methylene]-N-pentylhydrazinecarboximidamide, which has the generic name tegaserod and forms maleic acid salt (tegaserod maleate). Tegaserod and related compounds are serotonin 5HT<sub>4</sub>-receptor partial agonist and useful in the treatment of irritable bowel syndrome and other utilities as described in EP Patent No. 0 442,378.

20

Crystalline forms of tegaserod maleate have not been reported in the literature and also, the preparation of tegaserod maleate has not been described. So, there is a need for stable polymorphs of tegaserod maleate for better pharmaceutical preparations.

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It has now been discovered that tegaserod maleate can be prepared in four different crystalline forms.

Thus the object of the present invention is to provide stable novel crystalline forms of tegaserod maleate, processes for preparing these forms and pharmaceutical compositions containing them.

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### DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of tegaserod maleate, designated as Form I, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 5.3, 5.9, 6.4, 10.7, 16.1 and 26.8 degrees. Figure 1 shows typical Form I x-ray powder diffraction pattern.

In accordance with the present invention, a process is provided for preparation of tegaserod maleate Form I. In this process, maleic acid is added to a solution of tegaserod free base in acetone and tegaserod maleate Form I is isolated from the mixture. Tegaserod maleate Form I may be isolated by usual techniques like cooling, partial removal of the solvent from the solution, adding an anti-solvent.

In accordance with the present invention, an alternative process is provided for preparation of tegaserod maleate Form I. According to this process, tegaserod maleate is mixed with acetone and collecting tegaserod maleate Form I from the mixture by filtration. In this process any of the crystalline forms of tegaserod maleate may be used.

In accordance with the present invention, there is provided a novel crystalline form of tegaserod maleate, designated as Form II, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 5.3, 6.4, 6.9, 7.8, 8.7, 10.2, 10.8, 15.5, 16.8, 17.0, 19.5, 21.2, 21.7, 22.7 and 25.2 degrees. Figure 2 shows typical Form II x-ray powder diffraction pattern.

In accordance with the present invention, a process is provided for preparation of tegaserod maleate Form II. In this process, tegaserod maleate is dissolved in methanol and tegaserod maleate Form II is precipitated from the solution by adding acetonitrile. In this process any of the crystalline forms of

tegaserod maleate may be used may be used to prepare the solution in methanol.

In accordance with the present invention, there is provided a novel crystalline form of tegaserod maleate, designated as Form III, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 7.0, 7.9, 8.7, 10.2, 15.6, 15.9, 17.0, 19.5, 25.3 and 27.1 degrees. Figure 3 shows typical Form III x-ray powder diffraction pattern.

In accordance with the present invention, a process is provided for preparation of tegaserod maleate Form III. In this process, maleic acid is added to a solution of tegaserod free base in methanol and the contents are maintained for about 30 minutes at about 20°C to 25°C and then the crystals are collected by filtration.

In accordance with the present invention, another process is provided for preparation of tegaserod maleate Form III. According to this process, tegaserod maleate is dissolved in methanol and the solution is maintained for about 30 minutes at about 20°C to 25°C and then tegaserod maleate Form III crystals are collected by filtration.

In accordance with the present invention, there is provided a novel crystalline form of tegaserod maleate, designated as Form IV, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 6.9, 8.0, 10.3, 16.5, 19.6, 20.4, 20.9, 22.0, 23.2, 25.4, 28.0 and 28.7 degrees. Figure 4 shows typical Form IV x-ray powder diffraction pattern.

In accordance with the present invention, a process is provided for preparation of tegaserod maleate Form IV. In this process, maleic acid is added to a solution of tegaserod free base in methanol and tegaserod maleate Form IV is precipitated by adding methylene dichloride or isopropyl alcohol.

Tegaserod free base used in the above processes may be obtained by the procedures described in EP Patent No. 0 442,378.

In accordance with the present invention, there is provided a pharmaceutical composition comprising crystalline form of tegaserod maleate and a pharmaceutically acceptable carrier.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction pattern of tegaserod maleate Form I.

Figure 2 is a x-ray powder diffraction pattern of tegaserod maleate Form II.

Figure 3 is a x-ray powder diffraction pattern of tegaserod maleate Form III.  
Figure 4 is a x-ray powder diffraction pattern of tegaserod maleate Form IV.  
x-Ray powder diffraction spectrum was measured on a Siemens D5000 x-ray powder diffractometer having a copper-K $\alpha$  radiation.

5

The following examples further illustrate the invention.

#### Example 1

Tegaserod free base (10 gm) is dissolved in acetone (100 ml). Maleic  
10 acid (4 gm) is added to the solution and the contents are maintained for 1 hour  
at 25°C. The separated solid is filtered to give 12.5 gm of tegaserod maleate  
Form I.

#### Example 2

Tegaserod maleate Form II (5 gm) and acetone (70 ml) are mixed and  
15 refluxed for 1 hour and cooled to 25°C and filtered to give 4.8 gm of tegaserod  
maleate Form I.

#### Example 3

Tegaserod maleate Form I (10 gm) is dissolved in methanol (100 ml).  
Acetonitrile (150 ml) is added to the solution and the contents are heated to  
20 reflux. The contents are then cooled to 25°C and maintained for 30 minutes. The  
separated crystals are collected by filtration to give 9 gm of tegaserod maleate  
Form II.

#### Example 4

25 Tegaserod free base (10 gm) is dissolved in methanol (100 ml) and  
maleic acid (4 gm) is added to the solution. Then the contents are maintained for  
30 minutes at 25°C. Then the separated solid is filtered to give 13 gm of  
tegaserod maleate Form III.

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#### Example 5

Tegaserod maleate (5 gm) is dissolved in methanol (50 ml) and the  
solution is maintained at 25°C for 30 minutes. The separated crystals are  
collected by filtration to give 4.8 gm of tegaserod maleate Form III.

## Example 6

Tegaserod free base (10 gm) is dissolved in methanol (50 ml), maleic acid (4 gm) is added and the contents are refluxed for 30 minutes and then the resulting solution is cooled to 25°C. Methylene dichloride (200 ml) is added and  
5 the contents are maintained for 30 minutes at 25°C. The separated solid is collected by filtration to give 13 gm of tegaserod maleate Form IV.

## Example 7

Maleic acid (4 gm) is added to a solution of tegaserod free base (10 gm)  
10 in methanol (50 ml). The contents are maintained for 30 minutes at 25°C and isopropyl alcohol (150 ml) is mixed and contents are maintained for 30 minutes at 25°C. The separated solid is collected by filtration to give 12.5 gm of tegaserod maleate Form IV.

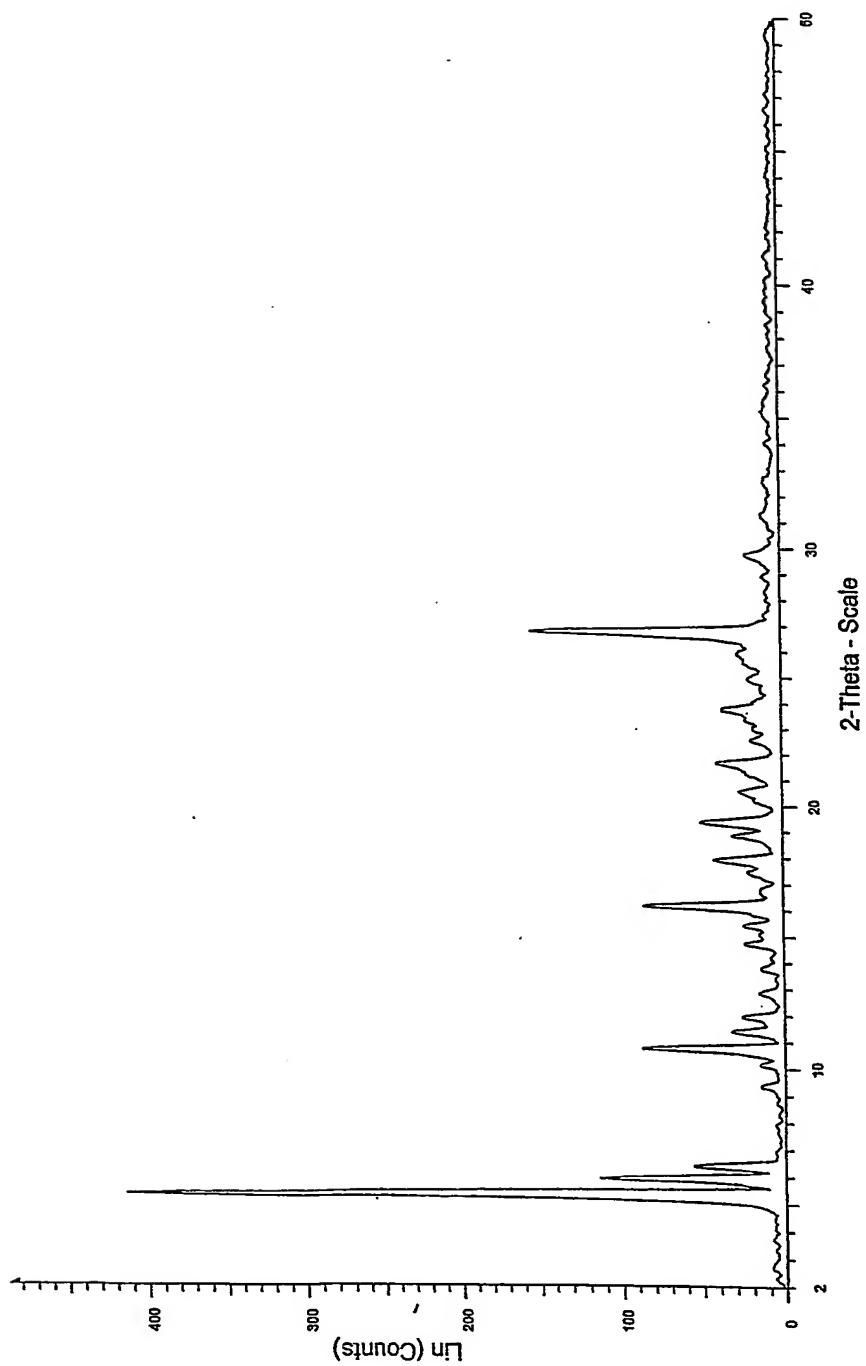
We claim:

1. A crystalline tegaserod maleate Form I, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 5.3, 5.9, 6.4, 10.7, 16.1 and 26.8 degrees.
2. A crystalline tegaserod maleate Form I as defined in claim 1, further characterized by an x-ray powder diffraction pattern as in figure 1.
3. A process for preparation of tegaserod maleate Form I as defined in claim 1, which comprises:
  - a) adding maleic acid to a solution of tegaserod free base in acetone; and
  - b) Isolating tegaserod maleate Form I.
4. A process for preparation of tegaserod maleate Form I as defined in claim 1, which comprises mixing tegaserod maleate and acetone and collecting tegaserod maleate Form I by filtration.
5. A crystalline tegaserod maleate Form II, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 5.3, 6.4, 6.9, 7.8, 8.7, 10.2, 10.8, 15.5, 16.8, 17.0, 19.5, 21.2, 21.7, 22.7 and 25.2 degrees.
6. A crystalline tegaserod maleate Form II as defined in claim 5, further characterized by an x-ray powder diffraction pattern as in figure 2.
7. A process for preparation of tegaserod maleate Form II as defined in claim 5, which comprises:
  - a) dissolving tegaserod maleate in methanol; and
  - b) precipitating tegaserod maleate Form II from the solution by mixing with acetonitrile;
8. A crystalline tegaserod maleate Form III, characterized by an x-ray powder diffraction pattern having peaks expressed as  $2\theta$  at about 7.0, 7.9, 8.7, 10.2, 15.6, 15.9, 17.0, 19.5, 25.3 and 27.1 degrees.
9. A crystalline tegaserod maleate Form III as defined in claim 8, further characterized by an x-ray powder diffraction pattern as in figure 3.
10. A process for preparation of tegaserod maleate Form III as defined in claim 8, which comprises:
  - a) mixing maleic acid and a solution of tegaserod free base in methanol; and
  - b) collecting the solid separated by filtration.

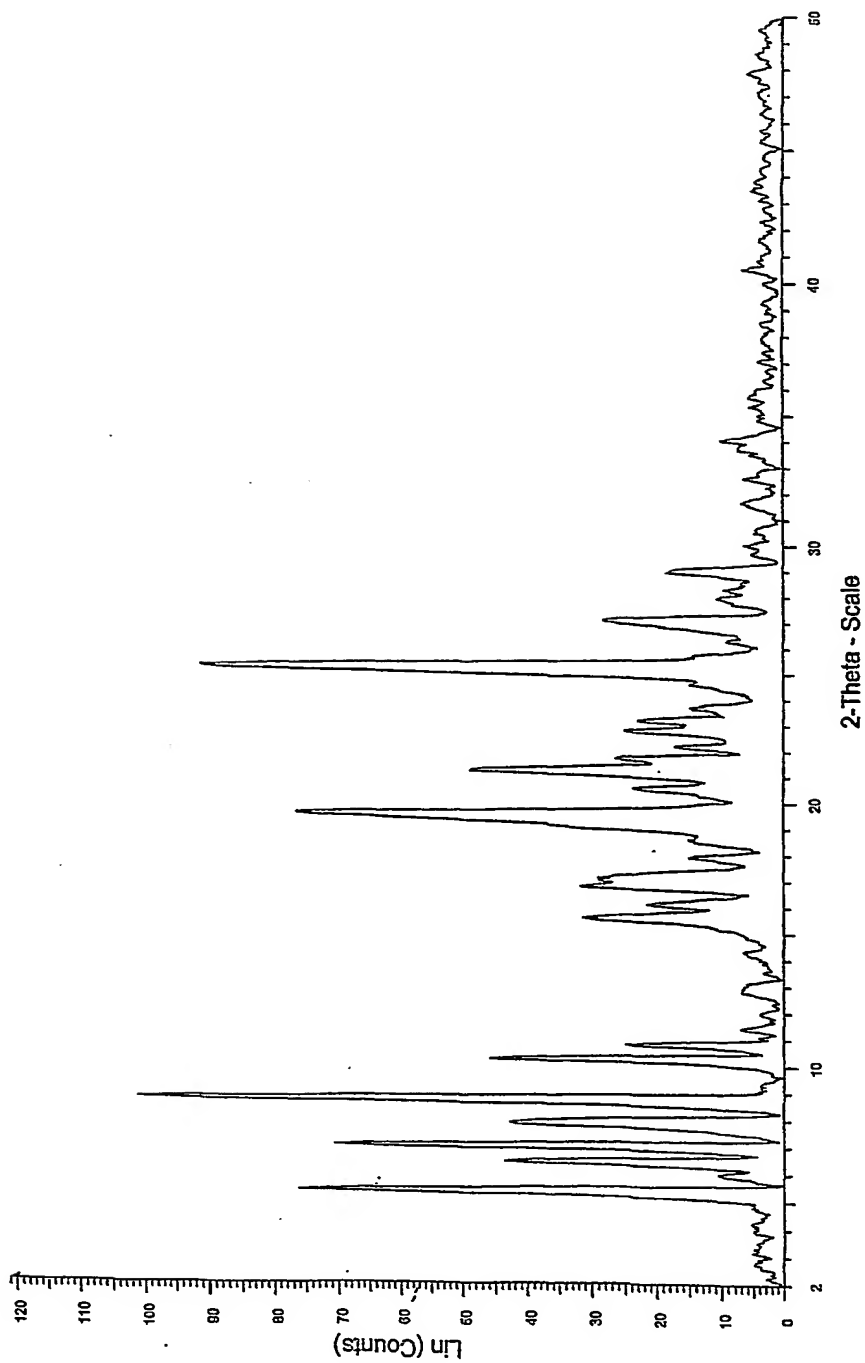


11. A process for the preparation of tegaserod maleate Form III as defined in claim 8, which comprises;
- a) dissolving tegaserod maleate in methanol;
  - b) maintaining for about 30 minutes at about 20°C to 25°C; and
  - 5 c) collecting the solid separated by filtration.
12. A crystalline tegaserod maleate Form IV, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 6.9, 8.0, 10.3, 16.5, 19.6, 20.4, 20.9, 22.0, 23.2, 25.4, 28.0 and 28.7 degrees.
13. A crystalline tegaserod maleate Form IV as defined in claim 12, further  
10 characterized by an x-ray powder diffraction pattern as in figure 4.
14. A process for preparation of tegaserod maleate Form IV as defined in claim 12, which comprises:
- a) mixing maleic acid and a solution of tegaserod free base in methanol; and
  - b) precipitating tegaserod maleate Form IV by mixing with methylene  
15 dichloride or isopropyl alcohol.
15. A pharmaceutical composition comprising crystalline form of tegaserod maleate and a pharmaceutically acceptable carrier.
16. A pharmaceutical composition as defined in claim 15, wherein the crystalline form is tegaserod maleate Form I of claim 1.
- 20 17. A pharmaceutical composition as defined in claim 15, wherein the crystalline form is tegaserod maleate Form II of claim 5.
18. A pharmaceutical compositions as defined in claim 15, wherein the crystalline form is tegaserod maleate Form III of claim 8.
19. A pharmaceutical compositions as defined in claim 15, wherein the  
25 crystalline form is tegaserod maleate Form IV of claim 12.

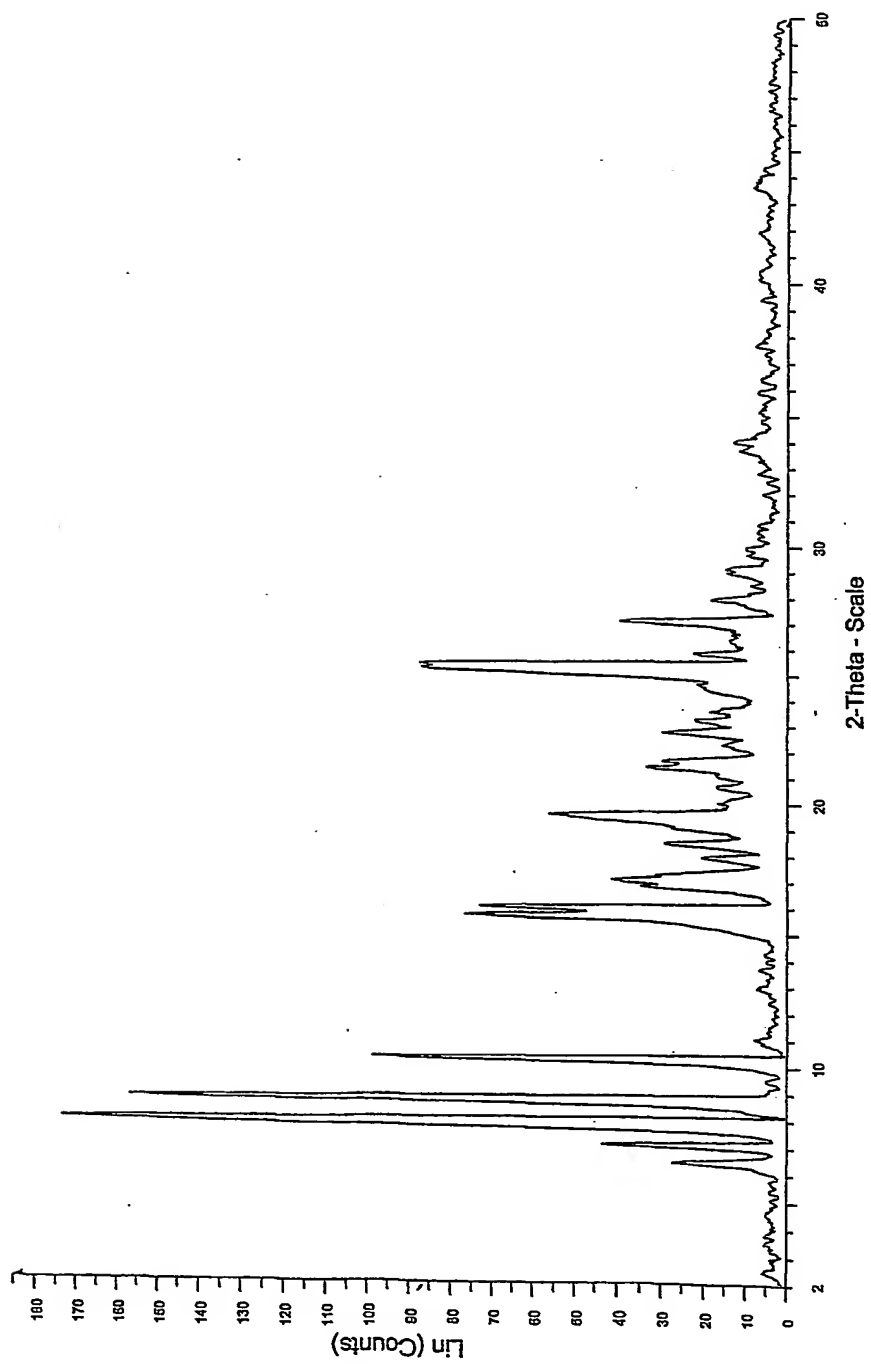
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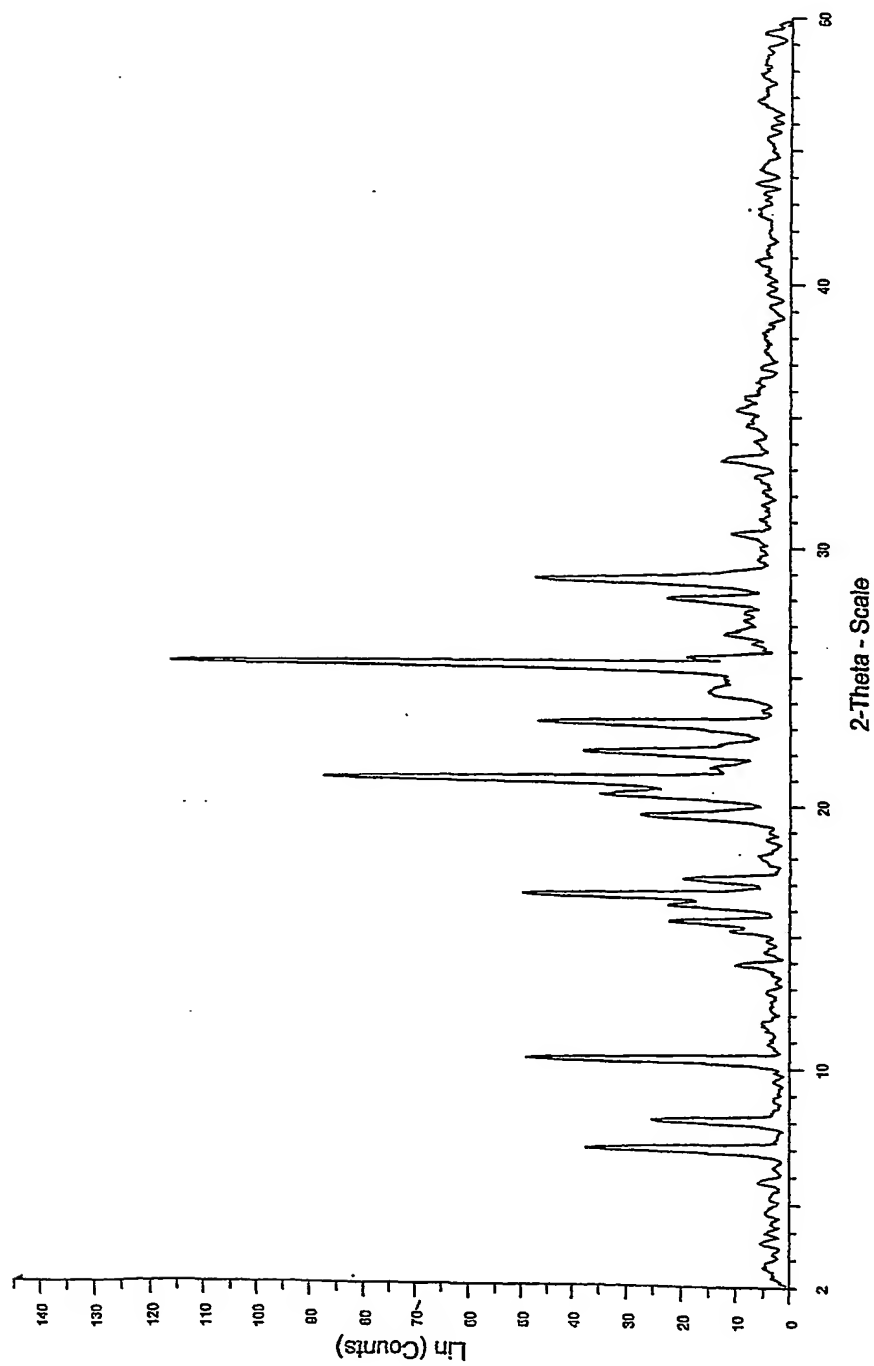


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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IN 03/00076-0

## CLASSIFICATION OF SUBJECT MATTER

IPC<sup>7</sup>: C07D 209/14; C07C 279/00; A61K 31/404

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC<sup>7</sup>: C07D, C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPOQUE, STN

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/10526 A2 (NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH) 2 March 2000 (02.03.00) <i>page 2, lines 18-31; page 3, lines 10-14; page 8, lines 19-22; examples 1-7; claims 7,17.</i>	1,3-5,7,8,10-12,14-19
X	GRAUL et al.: "Tegaserod maleate: 5-HT <sub>4</sub> Agonist, Prokinetic Treatment of Irritable Bowel Syndrome" Drugs of the Future, Prous Science, vol. 24, number 1, 1999, pages 38-44; ISSN: 0377-8282 <i>page 41, left column, paragraph 2.</i>	1,3-5,7,8,10-12,14-19
X	NOVARTIS: "Zelnorm (Tegaserod maleate)" Annotated Package Insert, Novartis Pharmaceutical Corporation, East Hanover, New Jersey [online] 22 July 2002 (22.07.02) [retrieved 10.11.2003]. Retrieved from the Internet <URL: <a href="http://www.fda.gov/cder/foi/label/2002/21200lbl.pdf">http://www.fda.gov/cder/foi/label/2002/21200lbl.pdf</a> > <i>page 1.</i>	1,3-5,7,8,10-12,14-19

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

„A“ document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA/AT

Austrian Patent Office

Dresdner Straße 87, A-1200 Vienna

Facsimile No. 1/53424/535

Authorized officer

KOLLER G.

Telephone No. 1/53424/458

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IN 03/00076-0

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 2,6,9,13  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Claims 2, 6, 9 and 13 refer to figures of the drawing and contravene Rule 6.2(a) PCT.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IN 03/00076-0

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
	A			none	
NO	A	V		none	
WO	A	010526		none	

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